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Tuberculosis and Aging: A Global Health Problem

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Despite the World Health Organization's declaration that the spread of tuberculosis is a global emergency and despite the implementation of strong tuberculosis-control initiatives, this highly infectious disease continues to affect all vulnerable populations, including the elderly population (age ⩾65 years). Tuberculosis in aging adults remains a clinical and epidemiological challenge. Atypical clinical manifestations of tuberculosis in older persons can result in delay in diagnosis and initiation of treatment; thus, unfortunately, higher rates of morbidity and mortality from this treatable infection can occur. Underlying illnesses, age-related diminution in immune function, the increased frequency of adverse drug reactions, and institutionalization can complicate the overall clinical approach to tuberculosis in elderly patients; maintenance of a high index of suspicion for tuberculosis in this vulnerable population is, thus, undoubtedly justifiable.

Tuberculosis remains a rampant infectious disease of global importance. The epidemiology of tuberculosis in developing and developed nations differs considerably [1]. Despite extensive tuberculosis-control efforts on the part of the World Health Organization and local health departments, the tuberculosis epidemic continues to ravage the developing world, affecting all susceptible individuals, including aging adults (age ⩾65). Developed countries, in contrast, have observed a steady decline in tuberculosis cases as a consequence of the overall implementation of more-efficient infection control practices, directly observed therapy (DOT), and immense efforts to suppress the HIV/AIDS epidemic; prevention and control strategies among other high-risk populations, such as the elderly population, however, still present a clinical and epidemiological challenge [2].

The geriatric population in developed countries, such as the United States, represents a large reservoir of tuberculosis infection across all ethnic and sex subsets. Clinical characteristics of tuberculosis in older adults can be unusual and may be confused with age-related illnesses [3]. Acute or chronic diseases, malnutrition, and the biological changes associated with aging can disrupt protective barriers, impair microbial clearance mechanisms, and contribute to the expected age-related diminution in cellular immune responses to microbes such as *Mycobacterium tuberculosis*. The diagnosis of tuberculosis can be difficult, and this treatable infection is sometimes documented only on postmortem examination. In addition, therapy for tuberculosis in elderly individuals is challenging because of the increased incidence of adverse drug reactions. Furthermore, institutionalized elderly persons are at especially high risk for reactivation of latent tuberculosis and are susceptible to new tuberculosis infection.

This article discusses the global epidemiology, pathogenesis, unique clinical consideration, diagnosis, treatment, and prevention of tuberculosis in aging adults, briefly highlighting the recent guidelines for targeted tuberculin testing and treatment of latent tuberculosis infection, as well as development of a tuberculosis vaccine.

GLOBAL EPIDEMIOLOGY

The World Health Organization estimates that 19%–43% of the world's population is infected with *M. tuberculosis* and that >8 million new cases and >2 million deaths from tuberculosis occur each year [1]. Ninety-five percent of tuberculosis cases occur in developing countries, as a result of limitations in resources that would ensure adequate treatment; HIV infection may also be common in such countries. In the United States and other industrialized nations, the recent success of tuberculosis control has been negated by the high burden of tuber-

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culosis among foreign-born persons; in the United States, nearly 40% of tuberculosis cases are among foreign-born individuals [4, 5]. Developed nations, including the United States, report an estimated 380 million persons infected with *M. tuberculosis;* ~80% of infected persons in Europe are ⩾50 years of age [2]. Similar increases in the incidence of tuberculosis have been demonstrated in association with advancing age in other regions of the world, such as Southeast Asia [2].

Although a significant percentage (80%–90%) of cases of tuberculosis in the elderly population occur among community dwellers (individuals living at home), there is a comparatively higher (2–3-fold) incidence of active tuberculosis among nursing home residents [6]. The enhanced transmissibility of tuberculosis within congregate settings, such as prisons, nursing facilities (nursing homes), chronic disease facilities, and homeless shelters, has raised concerns about tuberculosis infection and disease in the institutionalized elderly population [7]. Positive tuberculin reactivity has been demonstrated in association with prolonged stay among residents of long-term care facilities for elderly persons, implying that the risk of tuberculosis infection is higher in these settings [6, 7].

PATHOGENESIS AND IMMUNOLOGIC ASPECTS

Most descriptive analyses of the pathogenesis of tuberculosis come from Lurie and Dannenberg's studies in animal models [8, 9]. The following is a brief summary of these well-integrated disease mechanisms, relevant to the natural history and clinical course of tuberculosis in aging adults. The principal route of entry of *M. tuberculosis,* as well as the major organ of disease, is the lung. Bronchial airflow favors deposition of inhaled tubercle bacilli in the basal segments of the lower lobe, middle lobe, lingula, or anterior segments of the upper lobe, called the "primary infection segments." Inhaled tubercle bacilli are engulfed by alveolar macrophages and transported to regional lymph nodes. Infected macrophages and circulating monocytes secrete proteolytic enzymes, generating an exudative lesion. Activated mononuclear phagocytes incite granuloma formation with eventual activation of T cells; this leads to the onset of cell-mediated immune and delayed-type hypersensitivity responses, which are associated, in clinical context, with a positive dermal reactivity to standard-dose tuberculin antigen.

Because the major component of the immune system affected by senescence is the T cell–mediated response, dermal reactivity to tuberculin must be evaluated with caution (as detailed further in the Diagnosis section) [10]. The characteristic Ghon complex ultimately develops, consisting of organized collections of epithelioid cells, lymphocytes, and capillaries. Tubercle bacilli are confined and their growth restrained within caseous necrosis and surrounding fibrosis, with eventual healing. Reactivation (secondary or postprimary) tuberculosis is associated with granuloma liquefaction and rupture into the bronchoalveolar and vascular systems, promoting widespread microbial dissemination. Because animal model studies have clearly documented the relationship between age-related decline in T cell responses and the increased risk of infection by intracellular pathogens, including *M. tuberculosis,* it would appear that immunosenescence or immune dysregulation plays a role in the recrudescence of prior infection in elderly persons. However, other factors, including age-associated diseases (e.g., malignancy and diabetes mellitus), poor nutrition, immunosuppression, chronic renal failure, and chronic institutionalization, contribute to the increased risk of tuberculosis in the elderly population [3].

Approximately 90% of cases of tuberculosis disease that involve elderly persons are caused by reactivation of primary infection [3]. Tuberculosis infection without disease may occur in 30%–50% of individuals. Rarely, previously infected older persons may experience elimination of the viable tubercle bacilli and revert to a tuberculin-negative state and a "naive" immunologic status; these persons are at risk for new infection (reinfection) with *M. tuberculosis.* Thus, older persons potentially at risk for tuberculosis include individuals never exposed to *M. tuberculosis,* those with latent and dormant primary infection that may reactivate, and those who are no longer infected and thus are at risk for reinfection.

UNIQUE CLINICAL CONSIDERATIONS

Tuberculosis in older patients can present atypically [11, 12]. Approximately 75% of elderly persons with tuberculosis disease manifest lung involvement [13]. In addition, disseminated or miliary tuberculosis, tuberculous meningitis, and skeletal and genitourinary tuberculosis increase in frequency with advancing age [3, 14]. Many older patients with tuberculosis disease may not exhibit the classic features of tuberculosis (i.e., cough, hemoptysis, fever, night sweats, and weight loss). Tuberculosis in this population may present clinically with changes in functional capacity (e.g., activities of daily living), chronic fatigue, cognitive impairment, anorexia, or unexplained low-grade fever [11, 12]. Nonspecific symptoms and signs that range in severity from subacute to chronic and that persist for a period of weeks to months must alert clinicians to the possibility that unrecognized tuberculosis is present.

Pulmonary tuberculosis. Pulmonary tuberculosis is by far the most common form of tuberculosis in the elderly population [3, 11]. Although aging patients with pulmonary tuberculosis can present with typical respiratory as well as systemic symptoms (e.g., sputum production, hemoptysis, fever, night sweats, weight loss, and anorexia), a significant number of such patients may manifest atypical complaints or may exhibit minimal pulmonary symptoms. The radiographic manifestations

and variations of pulmonary tuberculosis in older persons are briefly described in the Diagnosis section.

Miliary tuberculosis. Miliary, or disseminated, tuberculosis occurs with greater frequency among aging patients; many cases are detected only at autopsy [15]. Miliary tuberculosis is typically associated with an acute or subacute pattern of high, intermittent fever and clinical evidence of meningeal or serosal involvement. Overwhelming infection results in numerous caseous lesions that harbor thousands of replicating tubercle bacilli and minimal neutrophilic infiltrate with no granulomatous reaction. Clinical features include unexplained fever, weight loss, and hepatosplenomegaly, without other focal signs; this form of tuberculosis should be considered in the differential diagnosis of fever of unknown origin.

Tuberculous meningitis. Tuberculous meningitis in elderly patients results from reactivation of a primary dormant focus or is associated with miliary seeding of infection [16]. Like younger patients, older patients generally present with a subacute onset of fever, headache, and confusion, with concomitant or preceding systemic symptoms of weakness, anorexia, and fatigue. However, some older patients can also manifest unexplained dementia or obtundation without fever or nuchal rigidity; for such patients, a high index of suspicion for tuberculous meningitis must be maintained until the suspicion is disproven. Tuberculous meningitis is associated with exceedingly high mortality among elderly persons; neurological sequelae or deficits are common among survivors.

Skeletal tuberculosis. In elderly persons, involvement of bone in *M. tuberculosis* infection commonly affects the spine [17, 18]. The thoracic and lumbar spines are commonly involved; cervical disease is unusual. Paravertebral abscesses, or cold abscesses, are often associated with spinal infection. Primary symptoms of spinal tuberculosis include pain over the involved vertebrae; neurological deficits and sinus tracts may occur with more advanced disease. Low-grade fever, weight loss, fatigue, and anorexia may be present. Tuberculous arthritis commonly involves the large, weight-bearing joints; however, in elderly persons, peripheral joints (i.e., the knees, wrists, ankles, and metatarsophalangeal joints) may be involved [19]. Pain and swelling of the involved joints and loss of range of motion can sometimes occur. Because older patients often have degenerative joint disease or other arthritides, the diagnosis of coexisting tuberculous arthritis may easily be overlooked.

Genitourinary tuberculosis. Although genitourinary tuberculosis occurs more often in persons in the third, fourth, and fifth decades of life, this form of disease is also seen in elderly persons [20]. The kidney is the major site of involvement, and as many as 20%–30% of patients are asymptomatic. Genitourinary tuberculosis may involve the ureters, bladder, prostate, epididymis, and seminal vesicles. Presenting symptoms may include dysuria, urinary frequency, flank pain, and hematuria. The diagnosis is often considered when an abnormal urinary sediment, pyuria without bacteruria, or hematuria is noted. Significant disease may result in pelvic or scrotal masses and draining sinuses; systemic manifestations (fever, anorexia, weight loss) may be absent.

Other sites. Tuberculosis in elderly patients, like that in younger patients, can involve almost any organ in the body. Tuberculosis disease involving the lymph nodes, pleura, liver, gall bladder, small and large bowel, pericardium, middle ear, and carpal tunnel has been described in older patients [3, 11].

DIAGNOSIS

For screening purposes, the tuberculin skin test remains the diagnostic intervention of choice, despite the associated potential for false-negative results. The prevalence of decreased relative strength of reaction or lack of reaction to tuberculin increases with age and may be partly explained by anergy. Moreover, the "booster effect" of skin-test reactivity to antigen increases in prevalence in the elderly population [21, 22]. Thus, it is essential that all older persons who undergo a tuberculin skin test (standard Mantoux method, using 5 tuberculin units of Tween-stabilized PPD, in which results are read 48–72 h after application) be retested within 2 weeks after a negative response (induration of <10 mm) is measured, to ensure that a potentially false-negative reaction is recognized.

A positive booster effect—and therefore a positive tuberculin skin test result—is a skin test reaction of $\geqslant$10 mm and an increase in induration of $\geqslant$6 mm in comparison with the first skin test reaction. A positive tuberculin skin test reaction after the initial application, resulting from the booster effect or conversion, or clinical manifestations suggestive of tuberculosis warrant chest radiography, because (as previously stated) 75% of all tuberculosis cases in the elderly population involve the respiratory tract. Most cases of pulmonary tuberculosis in elderly patients are reactivation disease; 10%–20% of cases result from primary infection or reinfection. Although reactivation tuberculosis classically involves the upper lobes of the lung (apical and posterior segments), several studies have shown that pulmonary tuberculous infection in many elderly patients manifests in either the middle or the lower lung lobes [3, 13]. Thus, clinicians must exercise caution when interpreting radiographic evidence of tuberculosis in older patients because of the possibility that infection may take hold in an atypical location in the lung fields.

Sputum examination for *M. tuberculosis,* using smear and culture, is indicated for all patients who have pulmonary symptoms and/or radiographic changes compatible with tuberculosis and who have not been treated with tuberculosis chemotherapy. More aggressive diagnostic intervention should be considered for elderly patients who are unable to expectorate sputum; the use of

Table 1. Regimens recommended for treatment of tuberculosis.

Option	Regimen
1	Isoniazid, rifampin, pyrazinamide, and ethambutol or streptomycin daily for 8 weeks, followed by isoniazid and rifampin daily or 2–3 times per week for 16 weeks (DOT)
2	Isoniazid, rifampin, pyrazinamide, and ethambutol or streptomycin daily for 2 weeks, followed by 2 times per week for 6 weeks (DOT), then isoniazid and rifampin 2 times per week for 16 weeks (DOT)
3	Isoniazid, rifampin, pyrazinamide, and ethambutol or streptomycin 3 times per week (DOT) for 6 months; consult a tuberculosis expert if the patient is still symptomatic or if smear or culture is positive for *Mycobacterium tuberculosis* after 3 months of treatment

NOTE. In areas where primary isoniazid resistance is <4%, omit the fourth drug. Streptomycin is not recommended for elderly individuals. Intermittent dosing should be directly observed. DOT, directly observed therapy. Data are from [27].

flexible fiberoptic bronchoscopy to obtain bronchial washings and bronchial biopsy specimens is clearly feasible and is a valuable diagnostic option [23]. In frail elderly patients, however, the risk of such a procedure should be carefully weighed against the benefit of potentially making a diagnosis of tuberculosis.

For suspected pulmonary tuberculosis, it is recommended that 3 fresh consecutive sputum specimens obtained in the morning be used for routine mycobacteriological studies [24]. These specimens should be subjected initially to smear examination and then cultured for *M. tuberculosis*. Because the finding of at least 10^4–10^5 acid-fast bacilli/mL of specimen is needed for microscopic detection by smear, this method is most useful for testing of sputum (which generally has the highest concentration of organisms) but can be applied to most other clinical specimens. Two acid-fast stains are most commonly used: carbolfuchsin (Ziehl-Neelson or Kinyoun) and fluorochrome (auramine-rhodamine). Routine mycobacterial culture methods (e.g., with Löwenstein-Jensen culture medium) that require up to 6 weeks for the growth of *M. tuberculosis* have been replaced by more rapid techniques that use radiometric systems, specific DNA probes, and PCR [25].

Nucleic acid amplification tests, such as PCR and other methods for amplifying DNA and RNA, may facilitate rapid detection of *M. tuberculosis* in respiratory tract specimens; recommendations for interpretation and use of the nucleic acid amplification test have been recently updated by the Centers for Disease Control and Prevention [26]. The rapid diagnosis of tuberculosis is especially important in the high-risk elderly population and for HIV-infected persons and patients infected with multiple-drug–resistant *M. tuberculosis* (MDR-TB). Histologic examination of tissue from various sites, such as the liver, lymph nodes, bone marrow, pleura, and synovium, that reveals the characteristic tissue reaction (caseous necrosis with granuloma formation) is also useful for diagnosis of tuberculosis disease.

TREATMENT AND PREVENTION

Treatment. Despite concern about the emergence of drug-resistant isolates of *M. tuberculosis* and the complex issue of how to treat tuberculosis in HIV-infected persons, the vast majority of cases of tuberculosis in elderly patients are caused by drug-susceptible strains of *M. tuberculosis* [3]. Evidence suggests that most cases of active tuberculosis in elderly patients result from reactivation of latent infection. These individuals presumably acquired the infecting organism before the availability of effective antituberculous chemotherapy. Hence, except for older patients who are from a country or region where the prevalence of drug-resistant *M. tuberculosis* is high, who previously have been inadequately treated with *M. tuberculosis* chemotherapy, or who acquired the infection from a contact known to be infected with MDR-TB, tuberculosis in elderly patients will be highly susceptible to isoniazid and rifampin.

Because the incidence of infection with MDR-TB has increased, tuberculosis treatment recommendations have been modified accordingly (table 1) [27]. In areas where isoniazid

Table 2. Criteria for positive tuberculin skin test reaction.

Induration	Criteria for positivity
⩾5 mm	HIV positive
	Recent contact with infectious tuberculosis
	Chest radiographic findings consistent with tuberculosis (e.g., fibrotic changes)
	Organ transplant recipient or other immunosuppressed person receiving prednisone (the equivalent of >15 mg/day for >1 month)
⩾10 mm	Recent arrival (<5 years) from high-prevalence country
	Injection drug user
	Resident of or employee[a] in a high-risk congregate setting: prison, jail, nursing or other health care facility, residential facility for AIDS patients, or homeless shelter
	Employee in mycobacteriology laboratory
	High-risk clinical conditions: silicosis, gastrectomy, jejunoileal bypass, body weight ⩾10% below ideal, chronic renal failure, diabetes mellitus, hematologic malignancy (e.g., lymphoma or leukemia), other specific malignancy (e.g., carcinoma of the head, neck, or lung), or alcoholism
⩾15 mm	No risk factors for tuberculosis

NOTE. Chemoprophylaxis is recommended for all high-risk persons, regardless of age. Data are from [24].

[a] For persons who are otherwise at low risk and are tested at the beginning of employment, ≥15 mm induration is a positive result.

Table 3. Drug regimens recommended for treatment of latent tuberculosis infection in adults, including elderly patients.

Drug	Interval and duration	Comments	Rating[a] for use in indicated patient group	
			HIV-negative	HIV-positive
INH	Daily for 9 months	In HIV-positive persons, INH can be given concomitantly with NRTIs, PIs, or NNRTIs. DOT must be used, with twice-weekly dosing.	A	A
	Twice weekly for 9 months	Same as above.	B	B
	Daily for 2 months	Not indicated for use in HIV-positive persons in whom fibrotic lesions are seen on chest radiography or for children. DOT must be used, with twice-weekly dosing.	B	C
	Twice weekly for 6 months	Same as above.	B	C
Rif + PZA	Daily for 2 months	May be substituted for INH in persons infected with INH-resistant, Rif-susceptible tuberculosis bacteria. In HIV-positive persons, PIs or NNRTIs generally should not be administered concomitantly with Rif; rifabutin can be used with indinavir, nelfinavir, amprenavir, ritonavir, efavirenz, nevaripine, or soft-gel saquinavir. DOT must be used, with twice-weekly dosing.	B	A
	Twice weekly for 2–3 months	Same as above.	C	C
Rif	Daily for 4 months	For use in persons who are intolerant to PZA and persons who are infected by INH-resistant, Rif-susceptible bacteria and are intolerant to PZA.	B	B

NOTE. DOT, directly observed therapy; INH, isoniazid; NNRTIs, nonnucleoside reverse-transcriptase inhibitors; NRTIs, nucleoside reverse-transcriptase inhibitors; PI, protease inhibitor; PZA, pyrazinamide; Rif, rifampin. Data are from [29].

[a] Rating: A, preferred; B, acceptable alternative; C, offer when A and B cannot be given.

resistance is ⩽4% or the population in question has a low risk for drug resistance (as do most older persons), the empirical 4-drug regimen is not necessary. Elderly persons are at greater risk for hepatic toxicity from isoniazid; this reaction, however, is relatively low in frequency and mild in severity [28]. It is recommended that clinical assessments and baseline liver function tests be performed before isoniazid and rifampin (and pyrazinamide) are administered to older persons; periodic laboratory monitoring seems prudent, particularly for frail elderly patients, who may not be able to communicate warning symptoms of drug toxicities.

An increase in the serum aminotransferase level to 5 times normal levels or clinical evidence of hepatitis necessitates the prompt withdrawal of isoniazid (as well as other hepatotoxic drugs); administration of these drugs may subsequently be resumed at lower doses and gradually increased to full doses according to the patient's tolerance. Relapse after drug rechallenge requires trial of an alternative regimen.

Chemoprophylaxis. Table 2 outlines the revised criteria for positive tuberculin skin test reactivity by size of induration necessitating tuberculosis chemoprophylaxis [24]. Recently published therapy guidelines for latent tuberculosis infection (LTBI) in adults, including elderly persons, are shown in table 3 [29]. Daily administration of isoniazid for 9 months has recently replaced the previously recommended 6-month schedule for treatment of LTBI. Randomized, prospective trials involving HIV-negative persons have indicated that a 12-month regimen is more effective than 6 months of treatment; subgroup analyses in several trials indicate that the maximal beneficial effect of isoniazid is likely to be achieved in 9 months, with minimal additional benefit gained by extending therapy to 12 months [29]. Although the 9-month regimen of isoniazid is preferred for the treatment of LTBI, the 6-month LTBI treatment course also provides substantial protection and has been shown to be superior to placebo in both HIV-positive and HIV-negative persons. Hence, clinical judgment must be exercised, taking into account local conditions, the experience of health departments or providers, cost, and compliance issues.

In a community-based study conducted in Bethel, Alaska, persons who took <25% of the prescribed annual dose of isoniazid had a 3-fold higher risk for tuberculosis than those who took >50% of the annual dose [30]. However, a more recent analysis of study data indicated that the efficacy decreased significantly if isoniazid was taken for <9 months [31]. Despite the fact that these new recommendations do not specifically address aging adults, recommendations for targeted skin testing and treatment of LTBI in high-risk populations must be extrapolated to include the elderly population.

Infection control issues. Enhanced awareness of drug-resistant tuberculosis has prompted public health agencies to institute strict guidelines for identification, isolation, treatment, and prevention of tuberculosis [4, 32–35]. The tuberculosis infection control program in most acute care and long-term care facilities should consist of 3 types of control measures:

administrative actions (prompt detection of suspected cases, isolation of infectious patients, and rapid institution of appropriate treatment), engineering controls (negative-pressure ventilation rooms, high-efficiency particulate air filtration, and ultraviolet germicidal irradiation), and personal respiratory protection requirements (masks) [4, 32, 33].

Vaccine development. Recent proceedings from the International Symposium on Tuberculosis Vaccine Development and Evaluation suggest that, although the development of novel vaccines for tuberculosis prevention is an area of immense interest to scientific researchers, public health agencies, and pharmaceutical manufacturers, there has been minimal success in developing a vaccine more effective than the BCG vaccine [35].

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